IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Benny Bang-Andersen, et al.
Application No.:	10/568,292
Filed:	August 14, 2006
Group Art Unit:	1624
Examiner:	Emily B. Bernhardt
Confirmation No.	3519
For:	TRANS-1-(6-CHLORO-3-PHENYLINDAN-1-YL)-3,3-DIMETHYLPIPERAZINE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

DECLARATION OF KLAUS GJERVIG JENSEN, Ph.D., UNDER 37 C.F.R. 1.132

I, Klaus Gjervig Jensen, hereby declare as follows:

1. I am a citizen of Denmark, more than twenty-one years of age.

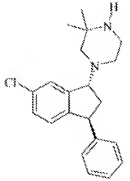
2. I received a Doctor of Philosophy degree in Epigenetics and Biotransformation from Department of Pharmacology, University of Copenhagen, Denmark in 1994.

3. I have been employed at H. Lundbeck A/S, the assignee of the present application, for over 15 years, holding positions of/as Biochemist and Section Leader, including my present position as Associate Director of Drug Metabolism and Pharmacokinetics (DMPK) in the Drug Absorption, Distribution, Metabolism and Excretion (ADME) Research department, which I have held since 2008. My curriculum vitae can be found at **Appendix A**, *infra*.

4. Benny Bang-Andersen, Klaus Peter Bøgeso, Henrik Svane, Lars Ole Lyngso, Allan Carsten Dahl, Mark Howells, Tomas Mow and I conceived of, and reduced to practice, the invention

claimed in the above-identified patent application, as to which we have been named co-inventors.

5. I have reviewed the above-identified patent application, which provides that the invention includes a compound, *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine of formula (I):



(I);

or a pharmaceutically acceptable salt thereof (hereinafter referred to as "Compound I").

6. I have reviewed the Final Office Action mailed February 3 2009, in connection with the above-identified patent application, along with the November 13, 2008 response to the May 13, 2008 Office Action, including the contemporaneously submitted declaration of my co-inventor, Benny Bang-Andersen ("the Bang-Andersen declaration"), pending claims for the application and amended claims being submitted with a Request for Continued Examination ("RCE") with which my declaration will be contemporaneously submitted.

7. I concur with and similarly declare the statements at paragraphs 4-22 of the Bang-Andersen declaration.

8. The CYP2D6 experiments were performed on different dates (*see* **Appendix** A of the Bang-Andersen declaration). Concerns have been raised on variability of the test results when comparing them over time (years). The enzyme source used was from the same supplier [BD Biosciences, San Jose, CA, USA] but from different batches. Inclusion of a positive control in

all experiments together with the certification issued by the supplier that the enzyme meets specifications allow for comparable results. Each chemical used was certified by the supplier [Sigma, St. Louis, MO, USA] as meeting its specifications. To ensure that the results are comparable over years, a positive control for CYP2D6 inhibition, Fluvoxamine, was included in each single run of the inhibition experiments. These values have been added to the table in **Appendix A** of the Baug-Andersen declaration (*see infra*, **Appendix B**), documenting consistent results. Although some variability are seen in the results, as with any other biochemical assay, these are in no way large enough to dismiss the differences seen.

9. Accordingly, the variability of the test results is not impacted by the fact that the results were obtained on different test dates. That is to say, the variability in the test results is real; and therefore, the unexpected, surprising and unpredictable finding that Compound I is a relatively weak inhibitor of CYP2D6 compared to structurally related Compounds A-H is not lessened because of the different test dates.

10. Because of the foregoing, Compound I and its aforementioned property is surprising, unexpected and unpredictable over the prior art Compounds A-H.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issued thereon.

01-03-2010
Date

Klaus Gjervig Jensen, Ph.D.

Exhibit A

CURRICULUM VITAE, KLAUS GJERVIG JENSEN, Ph.D.

Education
List of relevant educational background:

Year	Education	Education Institution
1990	M.Sc. (Cand. Scient. Biology/Chemistry)	Department of Environmental Medicine, University of Odense, Denmark.
1994	Ph.D.	Department of Pharmacology, University of Copenhagen, Denmark.

Professional Experience
List of professional experience supporting the job role:

Period	Position / Company / Major responsibilities
1994	Research fellow, Department of Occupational Medicine. National Institute of Occupational Health, Stockholm, Sweden
1994 -2000	Biochemist, Department of Drug Metabolism, H. Lundbeck A/S, Valby, Denmark.
2000 -2001	Biochemist, Department of Discovery ADME, H. Lundbeck A/S, Valby, Denmark.
2001-2006	Section Leader, Department of Discovery ADME, In Vitro ADME, H. Lundbeck A/S, Valby, Denmark.
2007-2008	Senior specialist, Department of Discovery ADME, In Vitro ADME, H. Lundbeck A/S, Valby, Denmark.
2008-?	Associate Director (DMPK), Drug ADME Research, H. Lundbeck A/S, Valby, Denmark.

Membership of Professional Societies
List of relevant memberships:

Year	Society
	ISSX
	AAPS

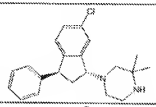
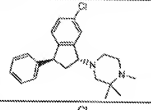
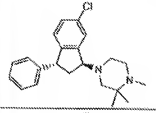
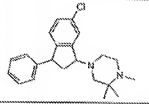
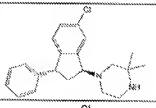
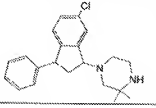
Publication / Presentation
List of relevant Publications / Presentation:

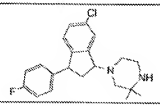
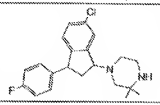
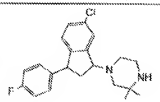
Year	Publication
1990	Jensen K.G., Andersen, O., Ronne, M. 1990. Spindle inhibiting effects of organotin compounds. Effects of trimethyltin on chromosome length. Scandinavian cell toxicology congress 9. ATLA. 17, 195-198.
1989	Jensen K.G., Andersen, O., Ronne, M. 1989. Spindle inhibiting effects of organotin compounds II. Induction of chromosomal supercontraction by alkyl and aryl compounds. Applied Organometal. Chem. 3, 225-229.
1990	Jensen K.G., Andersen, O., Ronne, M. 1990. Organotin compounds induce aneuploidy in human peripheral lymphocytes *in vitro*. Mutation Research. 246. 109-112.
1991	Jensen K.G., Andersen, O., Ronne, M. 1991. Direct and indirect assessment of aneuploidy inducing potency of organotin compounds. ATLA. 19, 214-218
1991	Jensen K.G., Önfelt, A., Wallin, M. Lidums, V. and Andersen, O. 1991. Effects of organotin compounds on mitosis, spindle structure, toxicity and in vitro microtubule assembly. Mutagenesis, vol. 6 no. 5, 409-416
1993	Jensen K.G., Loft, S. Doehmer, J. and Poulsen, H.E. 1993. Metabolism of phenacetin in genetically engineered V79 Chinese hamster cultures expressing rat liver CYP1A2 compared to isolated rat hepatocytes. Biochem. Pharmacol. vol 45, no. 5, 1171-1173.
1993	Jensen K.G., Önfelt, A., Poulsen, H.E. Doehmer, J. and Loft S. 1993. Effects of Benzo[a]pyrene and and (±)-*trans*-7,8-Dihydroxy-7,8-dihydrobenzo[a]pyrene on mitosis in Chinese hamster V79 cells with stable expression of rat cytochrome P4501A1 or 1A2. Carcinogenesis, vol 14, no. 10, 2115-2118.
1993	Fischer-Nielsen, A., Loft, S. and Jensen, K.G. 1993. Effects of ascorbate and 5-aminosalicylic acid on light induced 8-hydroxydeoxyguanosine formation in V79 Chinese hamster cells. Carcinogenesis vol. 14, no. 11, 2431-2433.
1995	Jensen K.G., Loft, S., Doehmer, J. and Poulsen, H.E. 1995. Kinetics and inhibition by phenacetin O-deethylation in V79 cells expressing human CYP1A2. Pharmacol. Toxicol. 76, 286-288.
1996	Parry, J.M., Parry, E.M., Bourner, R. Et al. 1996. The detection and evaluation of aneugenic chemicals. Mutat. Res. 353, 11-46.
1996	Jensen K.G., Poulsen, H.E., Doehmer, J. and Loft, S. 1996. Paracetamol-induced spindle disturbances in V79 cells with and without expression of human CYP1A2. Pharmacol. Toxicol. 78, 224-228.
1996	Loft, S., Jensen, K.G., Ringby, I., Poulsen, H.E. and Doehmer, J. 1996. Kinetic studies in engineered V79 Cells in comparison with primary hepatocytes and human liver microsomes. Exp. Toxic. Pathol. 48, Suppl. II, 249-256.
1999	Jensen,K.G. and Dalgaard, L. 1999. In Vitro Metabolism of The M1-Muscarinic Agonist 5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine by Human Hepatic Cytochromes P450 determined at pH 7.4 and 8.5. Drug Metab. Dispos. 27, No.1 ,125-132.

Publication / Presentation
List of relevant Publications / Presentation:

Year	Publication
1999	Christensen, E.B., Andersen, J.B., Pedersen, H. Jensen, K.G. and Dalgaard, L. 1999. Metabolites of [^{14}C]-5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine in Mice, Rats, Dogs and Humans. Drug Metab. Dispos. 27, No. 11, 1341-1349.
2000	Jensen, K.G., Wiberg, K., Klasson-Wehler, E. and Önfelt, A. 2000. Induction of aberrant mitosis with PCBs: particular efficiency of 2, 3,3',4,4'-pentachloro-biphenyl and synergism with triphenyltin. Mutagenesis Jan; 15(1): 9-15.
2004	Balle, T. Halldin C., Andersen, L., Alifrangis, L. H., Badolo, L., Jensen, K. G. Yuan-Wha Chou, Andersen, K, Perregaard, J. and Farde, L. 2004. New alpha-1-Adrenoceptor Antagonists Derived from the Antipsychotic Sertindole - Carbon-11 Labeling and PET Examination of Brain Uptake in the Cynomolgus Monkey. Nucl. Med. Biol. Vol 31/3, 327-336.
2009	Larsen, M; Holm, R; Jensen, KG; Brodin, B; Nielsen, CU. 2009. Intestinal gaboxadol absorption via PAT1 (SLC36A1): modified absorption in vivo following co-administration of L-tryptophan. British Journal of Pharmacology. Volume 157, Number 8, August 2009 , pp. 1380-1389(10)
2009	Elvang AB, Volbracht C, Pedersen LØ, Jensen KG, Karlsson JJ, Larsen SA, Mørk A, Stensbøl TB, Basilund JF.. 2009. Differential effects of gamma-secretase and BACE1 inhibition on brain Abeta levels in vitro and in vivo. J. Neurochem. 2009 Sep;110(5):1377-87.
2009	Larsen, M; Holm, R; Jensen, KG; Brodin, B; Nielsen, CU 5-hydroxy-L-tryptophan alters gaboxadol pharmacokinetics in rats: Involvement of PAT1 and rOat1 in gaboxadol absorption and elimination. European Journal of Pharmaceutical Sciences. 2009
2010	Jakob Jornil, Klaus Gjervig Jensen, Frank Larsen and Kristian Linnet . Identification of Cytochrome P450 Isoforms Involved in the Metabolism of Paroxetine and Estimation of Their Importance for Human Paroxetine Metabolism Using a Population-Based Simulator. Drug Metab. Dispos. 38, No.3 , 376–385, 2010

Appendix B

Compound ID	Compound Structure	Compound Name	CYP2D6 IC_{50} (μM)	Control CMP CYP2D6 (Fluvoxamine) IC_{50} (μM)	Test Date
Compound I		*trans*-1-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (enantiomer of Cpd E)	7.9* 5.4**	10.8* 8.1**	30-Aug-02* 20-Feb-03**
Compound A		*trans*-4-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (enantiomer of Cpd C)	0.1	2.8	20-Jul-01
Compound B		*trans* -4-((*1S,3R*)-6-chloro-3-phenyl-2,3-dihydro-1H-inden-1-yl)-1,2,2-trimethylpiperazine (enantiomer of Cpd C)	<0.02	7.8	20-Dec-06
Compound C		(±)-*trans*-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (racemate of Cpds A & B)	0.03	8.1	24-Aug-01
Compound D		*trans*-1-((*1S,3R*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (enantiomer of Cpd E)	0.2	2.6	3-Jun-03
Compound E		(±)-*trans*-1-(6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (racemate of Cpds I & D)	<0.05	2.1	24-Jul-01

Compound ID	Compound Structure	Compound Name	CYP2D6 IC_{50} (μM)	Control CMP CYP2D6 (Fluvoxamine) IC_{50} (μM)	Test Date
Compound F		*trans*-1-(6-chloro-3-(4-fluorophenyl)-indan-1-yl)-3,3-dimethylpiperazine (enantiomer of Cpd H)	1.3	10.9	3-Feb-03
Compound G		*trans*-1-(6-chloro-3-(4-fluorophenyl)-indan-1-yl)-3,3-dimethylpiperazine (enantiomer of Cpd H)	9	6.9	7-Aug-02
Compound H		(±)-*trans*-1-(6-chloro-3-(4-fluorophenyl)-indan-1-yl)-3,3-dimethylpiperazine (racemate of Cpds F & G)	2.7	6.9	25-Oct-04

*batch 1; **batch 2